

Prism Adaptation in a Case of Cerebellar Agenesis

by

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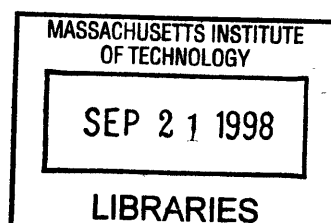
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Science

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ABSTRACT

Normal subjects adapt quickly to the displacing effects of prism goggles. A measure of this adaptation comes from the negative aftereffects in reaching that subjects show after the prism goggles are removed. Neural circuitry within the cerebellar cortex has been implicated as the site of plasticity for visuomotor adaptation. An opportunity to test a 15-year-old boy, A.C., with near complete cerebellar agenesis allowed us to determine whether cerebellar structures are critical for prism adaptation to occur. A.C. was tested on two separate occasions, twice using his left hand, and once using his right hand. He wore prism goggles while pointing to a vertical line at each of nine target locations in baseline, exposure, and postexposure conditions. The position of his finger was recorded after each response. In the exposure condition, the goggles were adjusted to 11° displacement to the right when A.C. pointed with his left hand, and to the left when he pointed with his right hand. He received visual feedback only in the exposure condition. His results were compared to those of 20 normal control subjects (NCS). Independent measures of performance and adaptation were calculated for left- and right-handed pointing by each subject. A.C. showed greater variability in pointing with his right (non-preferred) hand compared to his left hand and compared to NCS. An ordinal ranking indicated that his adaptation scores did not differ significantly from those of the NCS for either the left ($p = 0.30$) or right hand ($p = 0.22$). While these results do not disprove the theory that the cerebellum plays a role in normal adaptation, it does indicate that neural structures outside the cerebellum are sufficient to allow adaptation to occur.

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Thanks, Mom and Dad, for being there every step of the way.

This is dedicated to my dedicated other half, without whom, there would be no point.

Introduction

For normal subjects, accurately pointing to a visualized target is a relatively simple matter. The challenge of the task becomes greater when a subject is asked to point while viewing the target through goggles fitted with prism lenses. The effect of prism lenses is to bend the path of light entering the eye, creating a displacement between an object's perceived location and its actual location in space. A subject looking through the goggles, initially unaware of the displacement, will continue pointing with the same gaze-arm relationship and miss the target by an amount equal to the refraction of the light caused by the prisms. With repeated attempts, the subject eventually recovers accurate pointing and is said to have adapted to the effects of the prisms (Held and Hein, 1958; Harris, 1963). The most intriguing aspect of this experiment occurs after adaptation is achieved, the goggles are removed, and normal sensory conditions are restored: The subject shows a distinct aftereffect in pointing, missing the target by an amount equal to, but in the opposite direction of, the initial error when the goggles were first donned. This newly imposed error in reaching under normal conditions -- the negative aftereffect -- is evidence that a visuomotor recalibration has taken place, and that adaptation to the effects of the prisms is not simply a conscious cognitive correction.

Plasticity of synaptic strengths in the cerebellar cortex has been proposed as the underlying mechanism of adaptive motor learning (e.g., Thach, 1992; Ito, 1993). A theory originally formulated by Marr (1969) and extended by Albus (1971) hypothesized that, within the cerebellum, individual parallel fiber inputs to the output Purkinje cells represent

contextual information for motor associations. The strength of these associations can be modified through input from climbing fibers, whose firing serves as 'teaching' signals during the course of motor learning. Gilbert and Thach (1992) made extracellular recordings from Purkinje cells in macaque monkeys learning a motor adaptation task. They found that complex firing of the Purkinje cells, responses indicative of climbing fiber input, was positively correlated with the adaptation phase of the motor task. Further, these increases in complex firing were followed by decreases in Purkinje cell responses to parallel fiber input, indicating that these synaptic connections were strengthened through the course of learning the motor task.

The dependence of prism adaptation on intact cerebellar structures is also supported by studies of monkeys and humans with brain lesions. Baizer and Glickstein (1974) found that, of five monkeys with various cerebellar lesions, the animal with the largest lesion, while still able to perform the task of reaching for a food object, failed to show adaptation or a negative aftereffect in the arm ipsilateral to the lesion. Gauthier et al. (1979) looked at adaptation to magnifying spectacle lenses in human subjects with lesions of the posterior fossa. Of these subjects, one patient demonstrating persistent impairments associated with cerebellar dysfunction, was unable to adapt. Another study compared adaptation in patients with Parkinson's disease, cerebral hemispheric lesions, Korsakoff's syndrome, Alzheimer's disease, or cerebellar dysfunction (Weiner et al., 1983). Only the group of patients with cerebellar lesions showed both impaired adaptation in pointing while wearing the prism goggles, and diminished negative

aftereffects once the goggles were removed. More recently, Martin et al. (1996) sought to determine the specific areas within the cerebellum that are critical for adaptation to occur. They studied ball throwing while patients with lesions localized to different parts of the cerebellar system wore prism goggles. They found that "focal damage of the inferior olive, PICA (posterior inferior cerebellar artery) territory of inferolateral cortex, superior vermis, inferior or middle cerebellar peduncle, or basal pons all resulted in abnormal adaptation" (p. 1195).

We had the opportunity to examine the extent to which prism adaptation depends on the intact circuitry of the cerebellum when a young man born with essentially complete cerebellar agenesis was introduced to our laboratory. A.C. displayed a spectrum of cerebellar dysfunction similar to that described by Holmes (1939). Because A.C. showed obvious signs of cerebellar dysfunction not compensated for by remaining neural structures, we predicted that if adaptation is completely dependent on the specific organization of cerebellar cortex, then A.C. would not show adaptation to the effects of prism goggles.

Methods

Subjects

We tested 22 normal control subjects (NCS) from the M.I.T. community to establish a profile of prism adaptation in a neurologically unimpaired population. Subjects were 14 women and 8 men ranging in age from 19-39 years (mean age ± 1 SD = 24 ± 5 years), with a mean education level of 17 ± 3 years (range = 13-24 years). All but one were right-handed.

At the time of testing, A.C. was a 15-year-old boy in the seventh grade, with essentially complete cerebellar agenesis. Structural MRI scans of his brain (Figures 1A, B, C, D) show complete absence of the cerebellum, including the deep cerebellar nuclei, with the exception of a small nubbin of tissue at the left superior aspect (Figure 1B, 1C). Also absent are basilar pontine and inferior olivary nuclear prominences (Figure 1D). On neurologic examination, A.C. proved to be strongly left-handed and showed an array of classic cerebellar symptoms, including dysarthric speech, impaired eye movements with nystagmus, ataxic (uncoordinated) movements of the arms and legs (right more than left), and a clumsy gait with a slightly widened base. A.C. was tested on two separate occasions. Data were obtained from his left hand during both sessions, but were obtained from his right hand only during the second session due to his restlessness.

The experiment was approved by the M.I.T.'s Committee On the Use of Humans as Experimental Subjects. Signed consent forms were obtained from all subjects prior to testing. In the case of A.C., the consent form was also signed by his father. All subjects were naive to the purpose of the experiment and were paid for their participation

Materials

Subjects were seated in front of a 73.5 cm high table on which rested the testing apparatus (Figure 2). The apparatus was a 90 cm long x 35 cm deep x 25 cm high wooden table. Attached to the back of the table was a clear panel of Plexiglas that covered the full area below and 30 cm above the

tabletop. A removable section of the tabletop extended forward 12 cm from the edge of the Plexiglas and spanned the length of the apparatus. The movable target was a 50 cm long clear plastic T-square with a vertical black line extending along its length. The edge of the T-square rested on the top of the Plexiglas panel and could be moved to any position. From left to right across the Plexiglas panel were vertical lines at 1 cm intervals that the experimenter used to record the subjects' responses from behind the apparatus. Nine possible targets positions were marked on the Plexiglas at 5 cm intervals, 25 cm to 65 cm from the left edge of the apparatus with the 45 cm mark at the center of the table. A chin rest was attached to the larger table and aligned with the 45 cm mark on the apparatus.

The prism goggles were made from standard laboratory goggles with adjustable eyepieces. Each eyepiece consisted of two rotating glass wedge prisms that could be adjusted from 0 to 20 diopters laterally in either the left or right direction.

Procedure

In the baseline condition, subjects sat in front of the apparatus with their chins in the chin rest and the goggles set at 0° displacement. Subjects started each trial with their hands gripping the chin rest. The subjects were told to point in a ballistic manner below the tabletop to the vertical line, which was only visible to the subject above the tabletop. Each of the nine target positions was presented to the subject twice in a pseudo-random order. The experimenter recorded the position of the index finger on the Plexiglas wall with respect to the target.

In the exposure condition, the removable section of the tabletop was taken out to allow subjects visual feedback from their pointing. The goggles were adjusted for 11° displacement, and the subjects were asked to continue pointing to the target in the same ballistic manner as before. Each target was presented four times in pseudo-random order.

In the postexposure condition, the goggles were again adjusted to 0° displacement, and the section of the tabletop was replaced, preventing eye-hand visual feedback. Subjects again pointed in a ballistic manner to the nine targets, each presented four times in pseudo-random order.

The prisms were adjusted base right when the subjects pointed with their left hands, and base left when they pointed with their right hands.

Data Analysis

For statistical analysis we collapsed the data collected over two testing sessions for A.C.'s left hand performance. The performance score for the left and right hand of each subject was the mean standard deviation of response locations around the targets during the baseline condition. In order to obtain a quantitative measure of A.C.'s ability to perform the task, independent of his ability to adapt, we compared his performance scores to those of the NCS for the preferred and non-preferred hands.

To measure the negative aftereffect, and consequently the amount of adaptation shown by each subject, we compared the subject's pointing responses during the baseline condition with those during the postexposure condition. First, a delta score was calculated for the left and right hands of each subject by subtracting the mean baseline response difference (in cm)

from the four postexposure responses at each target position. An adaptation score was then computed separately, for each hand of each subject, by taking an inversely weighted average of the 4 delta scores (40% of response 1, 30% of response 2, etc.) by target position. This score allowed us to weigh the initial trials of the postexposure condition more heavily in the adaptation score than later trials. For the purpose of significance testing, we averaged the adaptation scores across all angles for each person, and then determined A.C.'s ordinal ranking relative to the NCS for left and right hand performance.

Results

We graphed left and right hand response profiles for the NCS as a group (Fig. 3A, B), and separately for A.C. (Fig. 4A, B), by plotting the location of each pointing response (averaged across NCS) sequentially by trial (abscissa), across all target angles (ordinate). For A.C. and the NCS, the direction of pointing during the exposure condition showed an initial deviation from baseline pointing, shifting to the right (downward on the graph) when the left hand was used with prisms base right, and to the left (upward on the graph) when the right hand was used with prisms base left. For the NCS, these deviations from the baseline occurred only during the initial trials of the exposure condition, and pointing became more accurate in the final trials of the exposure condition. For A.C., the same trends were observed, though his individual data were noisier than the averaged data of the NCS.

At the beginning of the postexposure condition, A.C. and the NCS again showed an initial shift in pointing direction, but opposite to that observed during the exposure condition. For the NCS, this shift in pointing direction lasted through the extent of the postexposure condition and did not return to baseline levels. A.C.'s individual data were too variable to reveal any patterns of decay of the negative aftereffects.

Performance Scores

We calculated performance scores to determine the variability of pointing for each subject (Table 1). For NCS using their preferred hand, the performance scores ranged from 0.9 to 3.4 cm, with an average performance score of 1.6 cm ($SD = \pm 0.6$). Performance scores of the NCS using their non-preferred hand ranged from 0.9 - 3.7 cm, with an average performance score of 1.8 cm ($SD = \pm 0.6$). A criterion of two standard deviations above the NCS performance score determined whether A.C.'s performance was impaired (Martin et al., 1992). A.C. had unimpaired pointing using his left (preferred) hand with a performance score = 2.3 cm, but was impaired at pointing with his right (non-preferred) hand with a performance score = 5.3 cm, a score greater than two standard deviations above the average NCS performance score.

Adaptation Scores

To compare A.C.'s ability to adapt with that of the NCS, we graphed scatterplots of the individual adaptation scores at each target angle separately for the left and right hands (Figs. 5A, B). A.C.'s adaptation scores,

connected by a line across each graph, fell within the ranges of the NCS adaptation scores for all angles. The averaged NCS adaptation scores range from 1.36 to 9.03 cm for left hand performance, and from -0.71 to -9.05 cm for right hand performance (Table 2). A.C.'s left hand adaptation score was 2.80 cm, and his right adaptation score was -2.95 cm. An ordinal ranking of the adaptation scores for all subjects showed A.C. to be the 7th least adapted for left hand pointing and the 5th least adapted for right hand pointing. The probability of A.C. getting these ordinal positions, assuming the null hypothesis that A.C. comes from the same distribution as the NCS, was determined by dividing his ranking by the total number of subjects. For his left hand performance, $p = 0.30$ (7/23), and for his right hand, $p = 0.22$ (5/23), indicating that his ability to adapt was not significantly different from that of the NCS at the $p = 0.05$ level.

Discussion

The ability to recalibrate the coordination of eye and hand while wearing prism goggles has been shown to be compromised by lesions within the cerebellar system (Weiner, 1983; Gauthier, 1979; Martin et al., 1996). These findings are in keeping with hypotheses that visuomotor adaptation occurs through changes in synaptic strengths within cerebellar cortex. It is, therefore, assumed that normal adaptation critically depends on intact cerebellar structures. In order to test this hypothesis, we examined prism adaptation in A.C., who was born with essentially no cerebellum.

A.C. and 22 NCS were asked to point to one of nine possible targets using either their left or right hands under baseline (without prism goggles),

exposure (with prism goggles), and postexposure (without prism goggles) conditions. Separate performance and adaptation scores were calculated as a means of assessing the possible contribution of motor impairments to impaired adaptation (Martin et al., 1996).

Contrary to our prediction, A.C.'s ability to adapt was not significantly different from that of the NCS when tested with either his left or his right arm, despite having impaired pointing accuracy when using his right arm. The dissociation between impaired performance and adaptation that A.C. showed when using his right arm has also been demonstrated in patients with specific cerebellar and cerebellar thalamic lesions (Martin et al., 1996), leading us to believe that this finding is real. The most convincing indication of A.C.'s ability to adapt came from examining the graphed response profiles for his left and right hands (Fig. 4A, B). A.C.'s responses reflected the trends observed in the averaged response profiles of the NCS (Fig. 3A, B), including the deviations in pointing, identifiable as the negative aftereffects that occur during the postexposure condition, after the prism goggles were removed. The results of this study indicate that A.C.'s existing neural structures are able to support visuomotor plasticity, and that he adapts to the effects of prism goggles in spite of the absence of cerebellar structures.

On the surface, the fact that A.C. showed visuomotor adaptation appears to stand in direct contradiction to proposals that the cerebellum is the neural substrate for adaptation. It is necessary, however, to use caution when attempting to extend results from a case of abnormal brain development to normal brain functioning. Plasticity in juvenile neural

structures has been well documented, and is exemplified by children who show full language and motor recovery after having surgical hemispherectomies to treat intractable epilepsy (Bach-y-Rita, 1990; Byrne and Gates, 1987). It is, therefore, reasonable to explain the results from this study as an outcome of functional plasticity. Reorganization within A.C.'s brain may have occurred so that functions normally performed by the cerebellum were acquired by existing neural structures, making prism adaptation possible. Interpreted most conservatively, it is possible that the findings from the present study, while interesting on their own, tell us nothing about adaptation in normal populations.

Yet, we propose that the results from this study, taken together with other experimental evidence, can provide insight into the neural basis of normal adaptation. First, there are no existing studies that examine whether reorganization within the cerebral hemispheres extends to the specialized circuitry of the cerebellum. While many locomotor functions are recovered after complete cerebellectomy in primates, the full extent of recovery is still open to question (Gilman et al., 1984). Previous case studies of subjects with complete or near complete cerebellar agenesis primarily describe neuroanatomical abnormalities post mortem (e.g., Warrington and Monsarrat, 1902; Priestly, 1920), but in cases where subjects lived to late childhood or adulthood, retrospective histories consistently describe delayed acquisition of motor skills and enduring cerebellar ataxia and dysarthria (Baker and Graves, 1931; Stewart, 1956). Glickstein (1994) reviewed accounts of cerebellar agenesis that report absences of associated motor symptoms. He concluded that "in all published cases in which

cerebellar agenesis is complete or near complete, there is evidence of severe motor deficit" (p. 1211). Similarly (and unlike the surgically treated children who show full recovery after hemispherectomies), A.C. continues to show striking deficits associated with cerebellar dysfunction. If extant neural structures can compensate for cerebellar functions, it is clear that they do not compensate for *all* cerebellar functions.

Second, there is evidence that monkeys and humans with lesions in brain structures other than the cerebellum also show impairments in prism adaptation. Macaques given frontal lobectomies or lesions to the caudate nucleus did not show reductions in prism-induced error when tested in a food reaching task, even though their performance was not impaired (Bossom, 1965). Paulsen et al. (1993) compared prism adaptation in patients with Huntington's disease or Alzheimer's disease matched for levels of dementia. In a task similar to the one used in the present study, the patients with Alzheimer's disease showed adaptation to the prism goggles and negative aftereffects when the goggles were removed, but the patients with Huntington's disease did not. Zeffiro (1995) used positron emission tomography (PET) to examine neural activation in normal subjects during the adaptation phase of a target-reaching task. Neural activation associated with adaptation was found not only in the cerebellum, but also in the ventrolateral thalamus and prefrontal cortex.

Together with the results from A.C.'s prism performance, these studies suggest that adaptive plasticity is more distributed than theories that promote the principality of the cerebellum in visuomotor adaptation would lead us to expect. Motor systems are distributed throughout spinal, brain

stem, subcortical, cortical, and cerebellar structures. The flexibility of motor programs at all levels would appear to be crucial for an animal's success in negotiating a constantly changing external environment. Auxiliary motor systems, such as the cerebellum or basal ganglia, could function to increase the gain of adaptation by centralizing error detection or end-goal modifications, but the site of plasticity could still lie at hierarchically lower levels. Under conditions of normal development, disruptions at the level of centralized functions would have freezing effects downstream, resulting in the impairments seen in patients with cerebellar and basal ganglia lesions. In cases of abnormal neural development, as seen in A.C., plasticity at lower motor levels, perhaps within the brainstem nuclei, may be sufficient to support prism adaptation. This theory suggests the possibility that A.C. has an upper limit to his ability to adapt which would be less than that of the NCS. Further studies that gradually increase the diopter strength of the prism goggles during adaptation to determine upper limits in A.C. and the NCS will allow us to answer this question.

The results of the present study do not disprove that the cerebellum plays a necessary role in normal prism adaptation, but they do add to evidence from other studies suggesting that the computations underlying visuomotor adaptation are not strictly confined to the cerebellum.

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Table 1 Performance scores for all subjects

Subjects	Preferred Hand	Nonpreferred Hand
RG	1.9	2.4
DW	3.7	3.0
SS1	1.7	3.4
JZ	1.4	1.8
KB	1.9	1.1
BW	2.0	2.0
HV	0.9	1.0
CG	1.5	1.5
HK	1.7	1.4
SN	2.2	1.5
RM1	2.6	1.1
SS2	1.2	1.7
RR	1.8	1.2
GM	1.8	0.9
DR	1.5	1.3
SF	2.5	1.5
JF	1.9	1.6
FG	1.3	1.2
JC	1.7	1.8
MD	1.1	1.2
JL	1.1	1.3
RM	1.7	1.1
Average	1.8	1.6
Range	0.9 - 3.7	0.9 - 3.4
Standard deviation	0.60	0.64
AC	2.4	*5.3

Performance scores were the mean standard deviation of response locations around the target during the baseline condition. *A.C.'s adaptation score was greater than two standard deviations than the average adaptation score of the NCS.

Table 2 Averaged adaptation scores for all subjects

Subjects	Left hand Mean (\pm SD)	Right hand Mean (\pm SD)
RG	2.7 (1.6)	-6.9 (1.5)
DW	2.9 (2.0)	-5.1 (2.7)
SS1	1.4 (1.2)	-3.3 (0.8)
JZ	2.4 (1.3)	-4.2 (0.8)
KB	2.0 (1.4)	-1.4 (1.6)
BW	5.2 (0.8)	-2.8 (1.4)
HV	6.1 (1.1)	-5.2 (1.2)
CG	5.4 (0.9)	-4.7 (1.4)
HK	4.4 (1.2)	-4.3 (1.6)
SN	4.3 (1.7)	-2.9 (1.5)
RM1	3.2 (0.6)	-3.5 (1.2)
SS2	3.0 (2.3)	-0.7 (1.3)
RR	4.9 (1.5)	-5.1 (1.7)
GM	5.5 (0.6)	-4.4 (1.7)
DR	4.5 (1.4)	-4.8 (1.4)
SF	7.2 (0.9)	-8.5 (1.0)
JF	4.2 (1.3)	-9.1 (1.2)
FG	9.0 (1.2)	-5.0 (1.4)
JC	2.6 (1.7)	-5.8 (0.7)
MD	3.5 (1.5)	-5.7 (0.8)
JL	3.9 (1.3)	-4.0 (1.0)
RM2	1.7 (0.9)	-3.5 (1.9)
Range	1.4 - 9.0	-9.0 - -0.7
AC	2.8 (2.7)	-3.0 (1.9)

Adaptation scores were the inversely weighted average of four delta scores calculated for each target. The delta score was the mean baseline response difference (in cm) from the four postexposure responses at each target position. The above scores represent the average adaptation score over all targets.

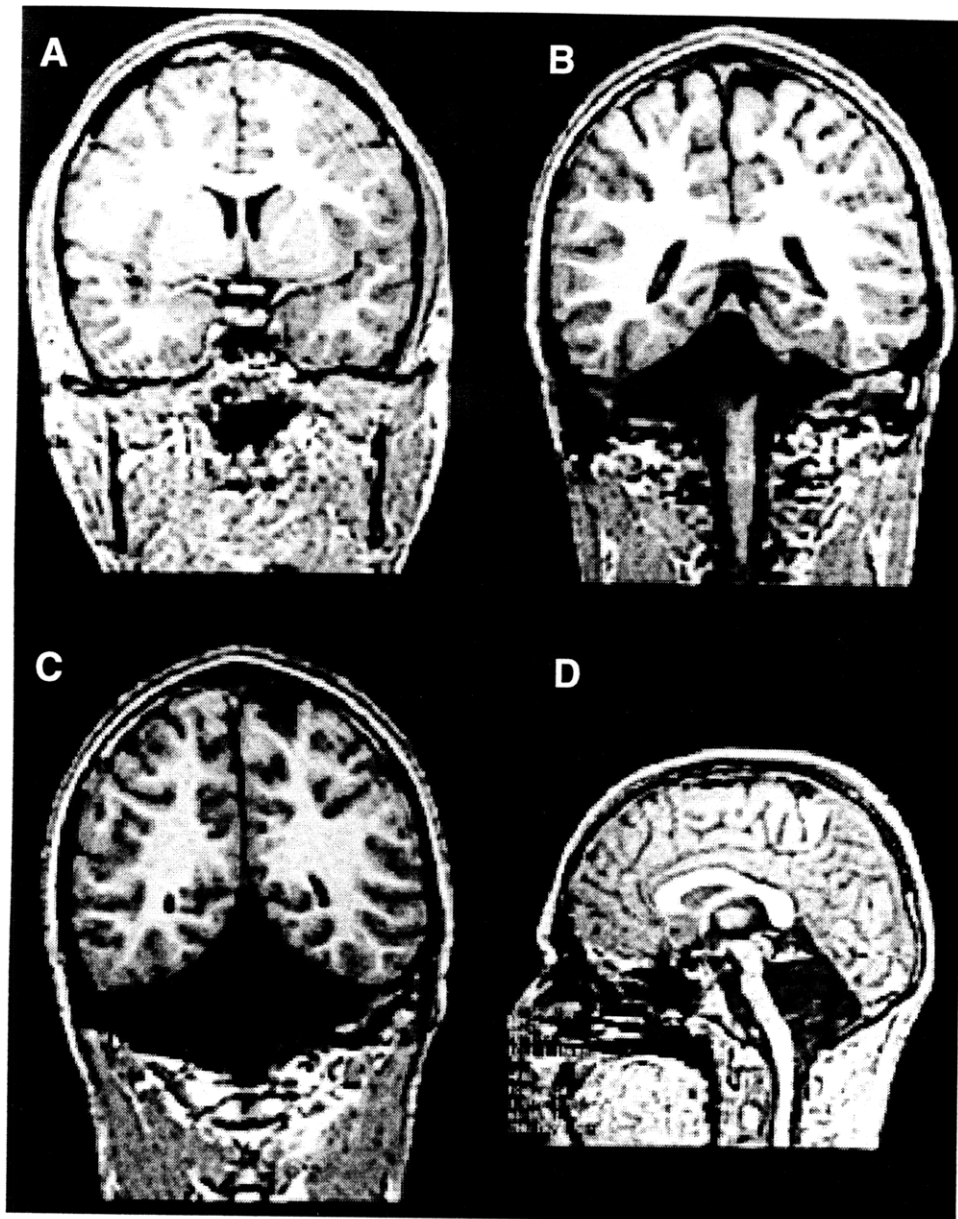


Fig. 1 Structural magnetic resonance images of A.C.'s brain. Subject's right is displayed on the left side. (A) Paracoronal section at the level of the forebrain. (B) Caudal coronal section showing absence of the cerebellum, including the deep cerebellar nuclei, in the posterior fossa. A small nubbin of cerebellum can be seen on the upper right side of the cavity (A.C.'s left). (C) Coronal section just caudal to B. (D) Midsagittal section. Cerebellar tissue can be seen just below the splenium of the corpus callosum. Note the absence of basalar pontine structures.

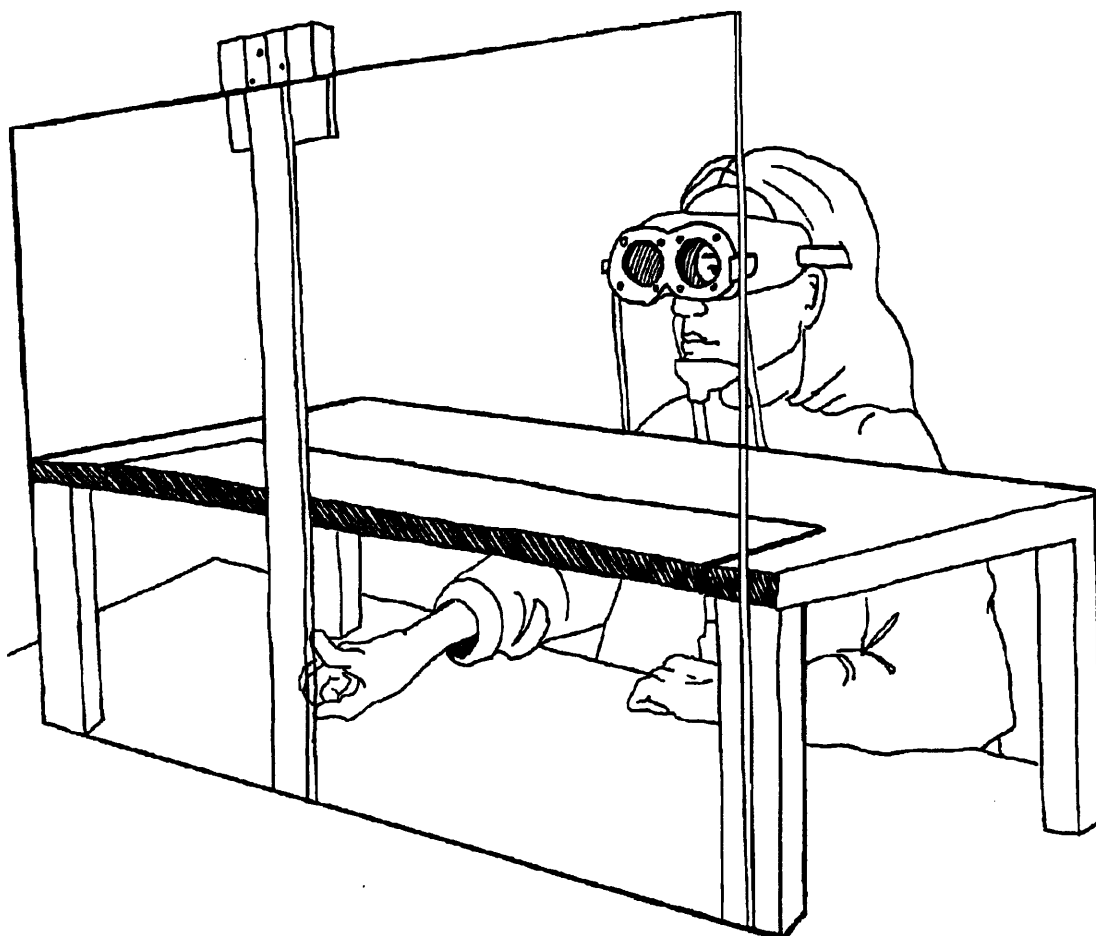


Fig. 2 Prism adaptation testing apparatus. Lines below the table used by the experimenter to measure the subjects' responses are omitted for clarity.

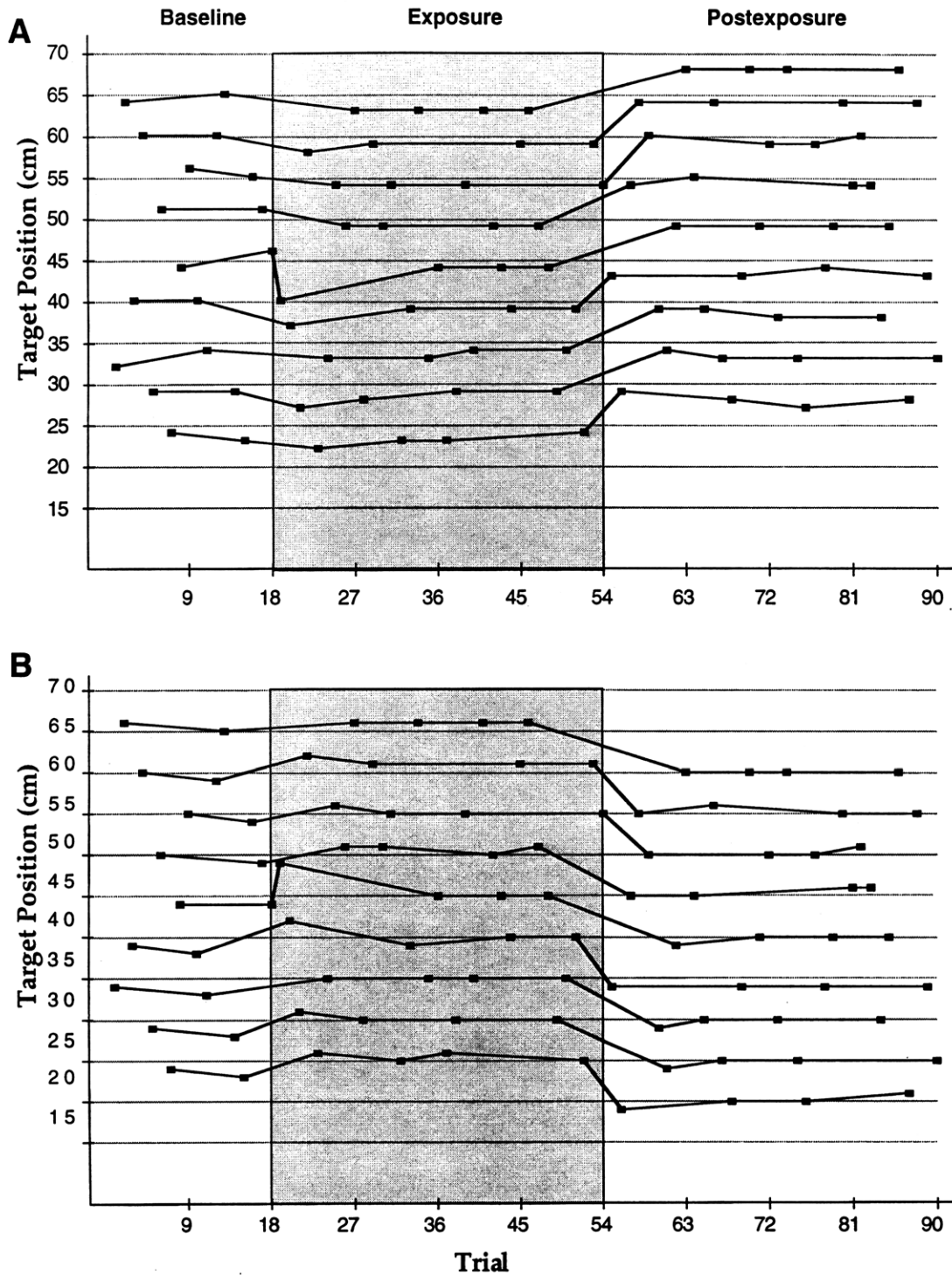


Fig. 3 NCS response profiles for left and right hands. Pointing responses, averaged across NCS ($n = 22$), are plotted sequentially by trial for each target angle. Error bars are omitted for clarity. **(A)** Left hand performance. **(B)** Right hand performance.

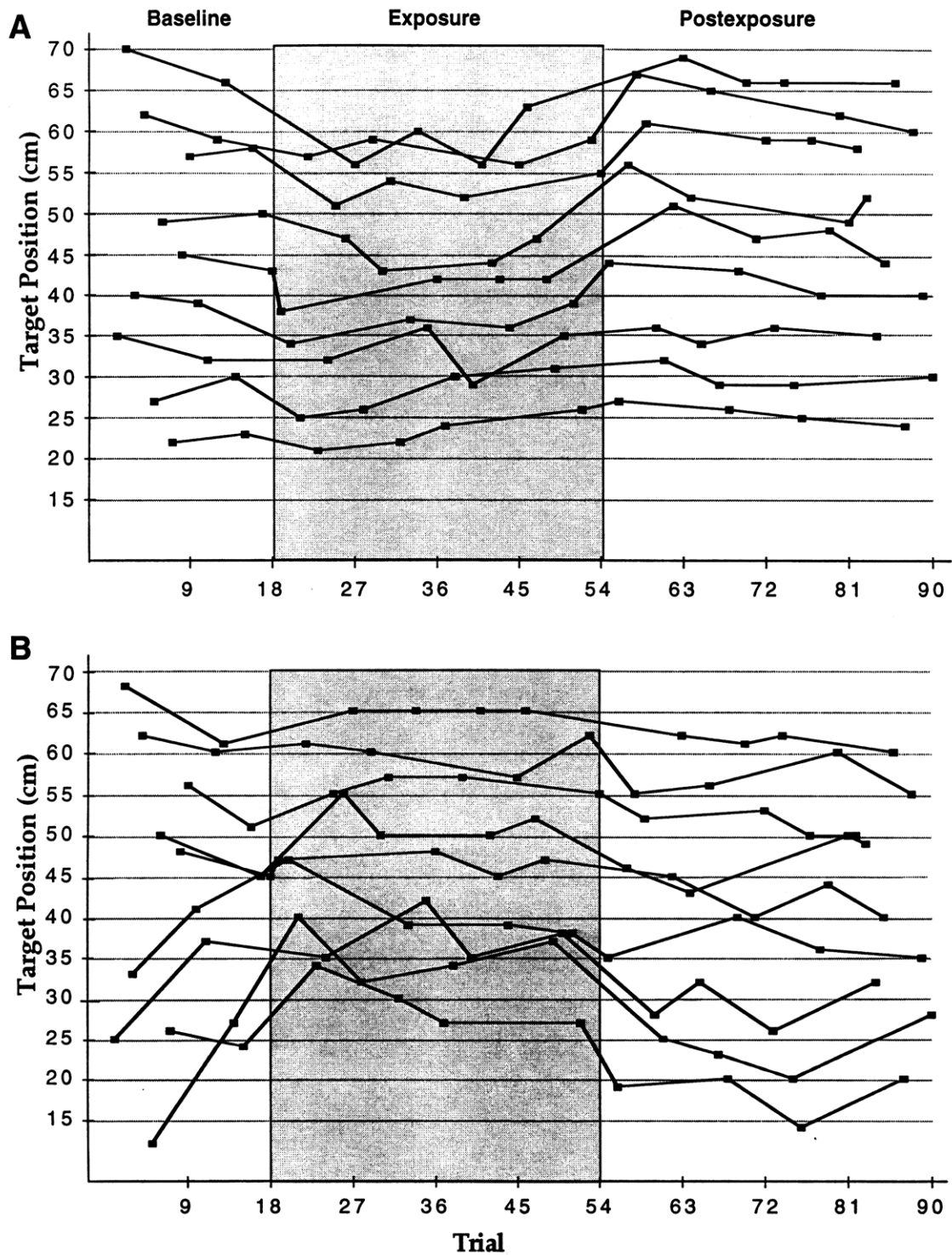


Fig. 4 A.C. response profiles for left and right hands. Pointing responses are plotted sequentially by trial for each target angle. **(A)** Left hand performance averaged over 2 testing sessions. **(B)** Right hand performance from 1 testing session.

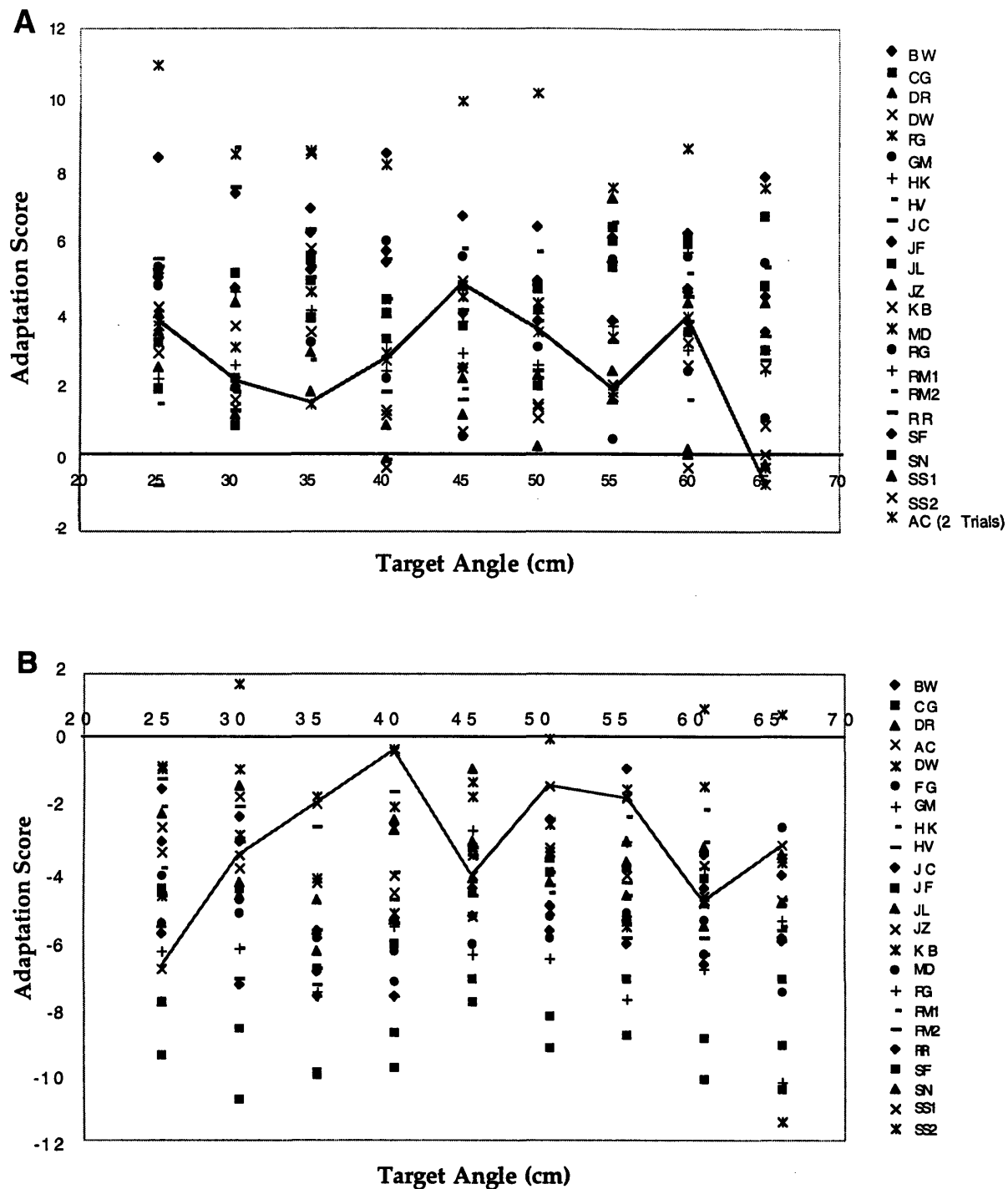


Fig. 5 Individual adaptation scores plotted across each target angle. A.C.'s adaptation scores are connected by the line.
(A) Left hand performance. **(B)** Right hand performance.